Iatrogenic Botulism After Botulinum Toxin Type A Injections

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Abstract: Therapeutic use of botulinum toxin type A (BT/A) is well known, effective, and safe. Iatrogenic botulism that presents with generalized weakness, dysphagia, and respiratory distress is a rare but significant complication in BT/A treatment. In this study, we report 4 patients who developed iatrogenic botulism after receiving therapeutic doses of BT/A for spasticity and blepharospasm. One patient was placed in intensive care unit, but consequently, every patient recovered fully. The cause of BT/A as an adverse effect is most likely hematological spread of the toxin.

Key Words: iatrogenic botulism, botulinum toxin A, spasticity, blepharospasm

(*Clin Neuropharm* 2010;33: 158–160)

Botulinum toxin type A (BT/A) is a potent neurotoxin. Botulinum neurotoxin is produced by the anaerobic bacterium *Clostridium botulinum*. It prevents the release of acetylcholine from presynaptic axons of the neuromuscular junction, and consequently, a dose dependent, reversible denervation develops in muscles. Botulinum toxin type A is commonly used for the treatment of focal dystonia and localized muscle spasticity. When used in therapeutic doses, the toxin is relatively safe and effective.[1] Systemic adverse effects are rare and include flu-like symptoms and fatigue.[2] Subclinical effects of botulinum toxin on neuromuscular transmission distant from the site of injection have been reported, as shown by increased jitter and frequent blockings on single-fiber electromyography (EMG).[3] Botulinum toxin type A may, in rare cases, cause generalized weakness. Cases of generalized botulism have been described after BT/A injections for cosmetic purposes or in extremities.[4–8]

In this report, we report 4 patients in whom treatment with therapeutic BT/A injections resulted in generalized botulism (Table 1).

CASE REPORTS

Case 1

A 31-year-old woman presented with long-standing hereditary spastic paraparesis (HSP) in August 2007. She had dysarthria, spastic gait, and a mild degree of weakness in the lower limb muscles. Her medical history was unremarkable except for HSP. Her father had spastic paraparesis. Botulinum toxin was injected for moderate spastic paraparesis. On her second injection session, she received a total of 1500 U BT/A (Dysport; [IPSEN BIOPHARM LTD, Wrexham, United Kingdom] 500 U in medial and lateral portions of the right, and 750 U in medial and lateral portions of the left gastrocnemii with 250 U in the left tibialis posterior muscle). Three weeks after the treatment session, she complained of a sudden onset of dysphagia and respiratory distress. Results of the neurological examination confirmed severe dysphagia, dysphonia, and severe weakness of the upper extremity. Aspiration pneumonia was detected. Antibacterial therapy was started. She had stertorous breathing and was intubated to protect her airway. She was administered pyridostigmine (240 mg/d) in divided doses, which produced some improvement in extremity and tongue strength. An EMG study was not performed. One month after the dysphagia and respiratory distress, she recovered fully.

Case 2

A 35-year-old woman presented with generalized dystonic spastic quadriparesis due to cerebral palsy. Her arms (left arm more than the right arm) were flexed at the wrist and elbow. Both were clearly dystonic. Her legs were marked spastic during the gait. She was not able to stand independently. She did not have any systemic and neurological disorders except cerebral palsy. There was no family history. The patient was treated with a total of 1000 U BT/A (Dysport), which was divided between the bilateral gastrocnemii (600 U), left tibialis posterior (100 U), and bilateral adductor muscles (300 U). Her spasticity somewhat improved; she was able to walk alone. She received 1500 U of Dysport in her leg muscles (300 U in the bilateral adductors, 500 U in the right gastrocnemius, 600 U in the left gastrocnemius, and 100 U in the left tibialis posterior muscle) at the third injection. One week after the injection, she had a diagnosis of dysphagia, dysarthria, and generalized, moderately severe weakness involving the neck, tongue, and trunk muscles. Treatment with pyridostigmine (120 mg/d) was started in divided doses. Her neurological symptoms and signs gradually improved over the next weeks, and 2 months later, she recovered fully. Electromyography was not performed.

Case 3

A 30-year-old woman with HSP presented with spasticity of the lower extremities. Results of the neurological examination confirmed spastic gait and moderately weakness of the bilateral gastrocnemii and tibialis posterior muscles. She was able to walk independently. She was treated with BT/A; a total 1000 U of Dysport were injected into the right and left gastrocnemius muscles, and a total 500 U into the right and left tibialis posterior muscles. Spastic gait improved considerably for about 2 months. The injections were repeated every 3 to 4 months using the same protocol and dosage schedule each time. One week after the fourth injection session, she developed fatigue, dysarthria, shortness of breath, dysphagia, and mild weakness involving the neck, tongue, masseter muscles and upper extremity muscles. Single-fiber EMG was performed in the right extensor digitorum communis muscle. Three of the pairs studied in the extensor digitorum communis showed excessive jitter without blockings. Test result for acetylcholine receptor antibodies was negative. She was given pyridostigmine (120 mg/d) in divided doses. For the next 6 months, she recovered fully.

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There was no financial supporting for this work.

DOI: 10.1097/WNF.0b013e3181d479e0

TABLE 1. Characteristics of the Patients

	Case 1	Case 2	Case 3	Case 4
Age,yr	31	35	30	74
Sex	Female	Female	Female	Female
Diagnosis	HSP	Spastic cerebral palsy	HSP	Blepharospasm
BT/A	Dysport	Dysport	Dysport	Dysport
Dose, U	1500	1500	1500	120
Signs of botulism	Respiratory distress, dysphagia, and generalized weakness	Dysphagia, dysarthria, and severe generalized weakness	Dysarthria, shortness of breath, dysphagia, and mild generalized weakness	Diplopia and fatigue
Outcome	Full recovery	Full recovery	Full recovery	Full recovery
BT/A injection resumed	No	Yes	Yes	Yes

Case 4

A 74-year-old woman presented with blepharospasm of 4 years. She received an injection totaling 120 U of BT/A (Dysport) from a 500 unit-vial, administered to the bilateral orbicularis oculi muscles. Ten days after the first injection, she experienced disturbances in her vision, bilateral weakness of visual acuity, diplopia, and fatigue. Results of the neurological examination confirmed impaired ocular movement with bilateral mild ptosis. Single-fiber EMG was abnormal in the right extensor digitorum communis muscle. Test result for acetylcholine receptor antibodies was negative. She improved spontaneously, and she was healthy as shown after a second single-fiber EMG by the end of the first month.

DISCUSSION

Botulinum toxin injection is the most common procedure performed worldwide, with an estimate of nearly 3 million injections per year.[9] In 2008, however, botulinum toxin serotypes A and B received bad press reviews. According to the Public Citizen's review of 180 reports of adverse effects related to botulinum toxin reported to the Food and Drug Administration (FDA), at least 87 people have been hospitalized and 16 killed because of a spread of the toxin beyond the injection site.[9,10] Four of the people who died from the injections were children. In the most serious cases, reported mostly in children treated for limb spasticity associated with cerebral palsy, outcomes included hospitalization and death. Moreover, respiratory distress and death were reported after the use of botulinum toxin types A and B for the treatment of a variety of conditions using a wide range of botulinum toxin doses for both FDA-approved and FDA-unapproved uses.[11] Adverse effects of the toxin leading to botulism-like features included dysphagia, dysphonia, muscle weakness, dyspnea, or respiratory distress.

Botulism is a rare paralytic and potentially fatal disease caused by *Clostridium botulinum*. Botulism is characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves. Blurred vision, dysphagia, and dysarthria are common initial complaints.[12] There are now 5 clinical categories of botulism[1]: classic or foodborne,[2] wound botulism,[3] infant botulism,[4] the hidden form (the adult variation of infant botulism),[5] and iatrogenic botulism, an unintended consequence of the treatment with BT/A.[13]

In this report, 4 patients demonstrated signs and symptoms consistent with botulism after intramuscular injections of therapeutic doses of BT/A. The symptoms of botulism occurred after the second or after the injection session in 3 of the patients, whereas, they occurred after only one dose of BT/A in the fourth patient. Neurologically, detectable weakness was present in the extraocular, bulbar, neck, trunk and upper/lower limb muscles. Clinical course and EMG findings in 2 patients (increased jitter on single-fiber EMG from extensor digitorum communis muscle) were suggestive of a disorder of neuromuscular junction.

Initial symptoms of botulism usually appear within a period ranging from 6 hours to 8 days; incubation period has been shown to correlate with the severity of the clinical course.[12–14] In our first case, the incubation period was long, but in 3 of them, it was 7 to 10 days.

It is well known that local injection of BT/A with therapeutic doses can effect neuromuscular junctions at distant sites.[4] The toxin probably circulates in the blood to produce blockade of transmitter release at both distant neuromuscular junctions and in the autonomic nervous system.[15] Possible mechanisms for the distant effects may be either a very efficient local uptake and retrograde axonal transport via spinal motor neurons or a systemic distribution via blood circulation.[16] Distant effects that appear in specialized EMG tests, such as weakness of distant muscles or generalized weakness, can also occur, possibly because of the toxin spreading in the blood.[4,5]

The total dose of the BT/A given averaged 1000 to 1500 (1000 U in case 3; 1500 U in cases 1 and 2) U of Dysport in cases 1, 2, and 3 and 120 U of Dysport in case 4, which is well below the maximum recommended dose.[5] The use by some authors of up to 5000 U of Dysport was not associated with adverse effects.[17,18] It is unlikely, therefore, that generalized muscle weakness resulted from an overdose of toxin in our patients. We hypothesize that an increased sensitivity to the BT/A in our patients (patients 1, 2, and 3), might be the cause of iatrogenic botulism. It is also possible that some of the BT/A was inadvertently injected directly into the capillary vessels (patient 4).

In this study, all cases of generalized botulism have been observed after injections of Dysport. The botulinum agents have different diffusion characteristics. Dysport, composed of a heterogeneous mixture of 500 to 900 kDa complex sizes, would be more likely to diffuse outside the target tissue compared with Botox (uniform 900 kDa complexes).[19] The potential for diffusion by product (ranging from lowest to highest) appears to be that Dysport is higher than Botox. Several factors influence diffusion, including preparation characteristics (eg, molecular size and structure), dosing and injection technique, intrinsic properties of the formulation (eg, protein load), and muscle injected.[20,21]

Generalized adverse reactions occurred after treatment of a variety of conditions using a wide range of botulinum toxin

doses as well as our cases. We reviewed the conditions and factors that facilitated iatrogenic botulism: None of the patients had history of use of antibiotics such as gentamicin, tobramycin, clindamycin, and lincomycin or heart medications such as quinidine, and none had history of myasthenia gravis. It is interesting that all cases were women. Jankovic and Schwartz[22] reported that women are more likely to develop complications, such as dysphagia and neck weakness, than are men in their study, which included 242 patients with cervical dystonia.[8,22] This condition may be speculated that women are more susceptible for overdose of botulinum toxin because they have less muscle bulk than men.

The patients have to be alerted to and educated about potential adverse events due to distant spread of toxin effects after local injection, including unexpected loss of strength or muscle weakness, dysphonia, dysarthria, loss of bladder control, trouble breathing or swallowing, blurred or double vision, and drooping eyelids. In addition, it must be kept in to mind that adverse events have been reported as early as several hours and as late as several weeks after treatment.

In conclusion, we have reported 4 patients who developed generalized botulism after local BT/A injections despite use of therapeutic doses. Although there was an absence of adverse effects at the initiation of treatment, botulism can occur sporadically after any therapeutic dose. Clinicians should be aware that systemic effects may occur with localized BT/A therapy and may be life-threatening. Regular long-term monitoring is essential in patients treated with BT/A.

ACKNOWLEDGMENT

The authors thank Sirin Artan-Kahrs, MD, for reviewing the manuscript.

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